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Interferon Alfa Versus Interferon Alfa Plus Cytarabine Combination Therapy for Chronic Myeloid Leukemia: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

OBJECTIVE: This article compares the effect of interferon alfa plus cytarabine (IFN-alfa + Ara-C) versus IFN-alfa alone on the chronic phase of chronic myelogenous leukemia.

METHODS: Electronic searches were performed in the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, Chinese Biomedical Database, China Journal Full-text Database, and Chinese Scientific Journals Database. The languages were limited to Chinese and English. Randomized controlled trials were selected by 2 investigators. Analyses were performed using RevMan 5.0 software.

RESULTS: A total of 3139 patients in 4 studies met the inclusion criteria. In those patients, complete hematologic response and cytogenetic responses showed significant improvements in favor of IFN-alfa + Ara-C, with complete hematologic response relative risk (RR) of 1.15 (95% CI, 1.09–1.21), complete cytogenetic response RR of 1.87 (95% CI, 1.47–2.38), partial cytogenetic response RR of 1.48 (95% CI, 1.25–1.75), and major cytogenetic response RR of 1.61 (95% CI, 1.42–1.83), respectively. The overall 3-year survival rate in the IFN-alfa + Ara-C group was 86% compared with 79% in the IFN-alfa group (RR = 1.09; 95% CI, 1.03–1.14). In the other 2 studies, 5-year overall survival was 69% compared with 63%, respectively (RR = 1.08; 95% CI, 1.01–1.15). However, IFN-alfa and Ara-C involved higher risk of hematologic toxicity, gastrointestinal adverse events, and severe mucositis compared with IFN-alfa monotherapy (RR = 2.63 [95% CI, 1.94–3.56); RR = 3.38 [95% CI, 2.28–5.00], and RR = 8.84 [95% CI, 3.82–20.46], respectively). Weight loss and skin rash were also observed more frequently in the combination treatment group (RR = 2.00 [95% CI, 1.47–2.73) and RR = 3.75 [95% CI, 2.13–6.59], respectively).

CONCLUSIONS: In patients with chronic myelogenous leukemia in the chronic phase, the combination of IFN-alfa + Ara-C demonstrated improved complete hematologic response, superior cytogenetic responses, and higher rates of 3- and 5-year survival than IFN-alfa alone. However, combination therapy is more likely to cause serious adverse effects. Well-designed studies will be required to determine the outcomes and adverse effects of the 2 drugs as treatment for patients with chronic

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myelogenous leukemia who cannot afford molecularly targeted drugs. (*Curr Ther Res Clin Exp.* 2011;72:150-163)

KEY WORDS: chronic myelogenous leukemia, cytarabine, interferon alfa, meta-analysis.

INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder that typically evolves through 3 clinical phases: chronic, accelerated, and blast crisis. The hallmark of CML, the Philadelphia (Ph) chromosome, is an abnormally short chromosome 22 that results from a balanced translocation t(9;22)(q34;q11). The translocation leads to the formation of a hybrid gene *BCR/ABL* that encodes for the fusion protein BCR/ABL, which results in deregulated tyrosine kinase activity.[1] Incidence rates vary from 0.6 to 2.0 cases per 100,000 inhabitants, increase with age, and are higher in men than in women.[2]

Before the advent of imatinib, the principal mode of CML treatment was palliative chemotherapy, mostly with busulfan and hydroxyurea. Hydroxyurea can achieve a hematologic response but not a cytogenetic response (CR).[3,4] For a minority of patients who are appropriate candidates with a suitable donor, curative bone marrow transplantation can achieve complete molecular remissions and cure,[5] even with continuing progress of this approach with unrelated donors, doctors are still greatly interested in drug treatment.

Interferon alfa (IFN-alfa) was introduced in the early 1980s but did not become widely accepted as primary treatment until several randomized studies[6–8] showed that IFN-alfa monotherapy provided a significant advantage when compared with conventional chemotherapy such as hydroxyurea and busulfan. Treatment induces a complete hematologic response (CHR) of 40% to 80%, a CR of 15% to 58%, a major cytogenetic response (MCR; ie, Ph <35%) of 30% to 50%, and a complete cytogenetic response (CCR; ie, Ph 0%) of 5% to 25%. The median survival rates range from 60 to 90 months. The positive effect of IFN-alfa on survival, mainly in low-risk patients, was confirmed by a meta-analysis of the randomized trials.[9]

Cytarabine (Ara-C) is an antimetabolite, isolated from the sponge *Cryptothetya crypta*, which is known to possess anti-CML activity.[10] Ara-C produced a superior outcome in patients with CML who have experienced treatment failure with IFN-alfa and should be investigated together with IFN-alfa as part of front-line CML therapy. Combination therapy with Ara-C and IFN-alfa in patients with chronic phase CML was shown to increase the rate of MCRs and prolong survival compared with treatment with IFN-alfa alone.[11] Continued research into the treatment of patients with CML has shown that achievement of a sustained CCR correlates with prolonged survival.[4,12]

The advent and success of imatinib therapy in CML have dramatically changed the CML therapeutic algorithm. The remarkably rapid and apparently durable control of hematologic features and the high rate of CR achieved with imatinib used as a single agent suggest that this drug could substantially prolong life.[13] However, response to

the drug varies among patients, and criteria are tentatively suggested for defining response and nonresponse or response failure. For example, after 5 years of follow-up in the International Randomized Study of Interferon and STI571, 5% of patients receiving imatinib withdrew from therapy or crossed over to the IFN-alfa + Ara-C arm because of adverse events.[4] Moreover, many patients in developing countries were prevented from receiving treatment with this targeted therapy drug because of its high cost. Notably, IFN-alfa or IFN + Ara-C was considered the best initial treatment for patients newly diagnosed with CML not eligible for allogeneic stem cell transplantation and those who cannot afford the cost of imatinib treatment. In daily clinical practice, physicians often encounter those types of patients, and these encounters are disconcerting for those who work in developing countries. These reports provide a summary of the efficacy and safety of IFN-alfa + Ara-C therapy in these unrelated donor patients or patients who cannot afford the higher cost of imatinib.

We therefore performed a meta-analysis to assess the long-term outcome of CML patients in the chronic phase who received IFN-alfa + Ara-C compared with those who were treated with IFN-alfa monotherapy.

METHODS

Inclusion criteria were as follows: (1) patients diagnosed with CML; (2) CML patients with chronic phase of the disease, who were found to be positive for the Ph chromosome; and (3) patients who had not previously been treated with chemotherapy, including hydroxyurea, busulfan, and IFN-alfa. Excluded patients were those: (1) with features of accelerated or blast phases of CML; (2) with a history of depressive illness or another psychiatric disorder or severe hepatic, renal, or cardiovascular disorders; (3) age >70 years; and (4) who initially failed to respond to tyrosine kinase inhibitor treatments.

Types of studies included in the analysis were randomized controlled trials (RCTs) with subgroup meta-analysis; they were included regardless of whether they provided information about concealment of allocation. Types of intervention analyzed was IFN-alfa + Ara-C versus IFN-alfa alone. Types of outcome measures examined: primary outcome factors, CHRs, CRs, MCRs, CCRs, and PCRs. Three- and 5-year survival rates were also assessed. Secondary outcome measures included toxicities and adverse effects (hematologic toxicity; nausea, vomiting, and diarrhea; mucositis; weight loss; fever, flu-like syndrome, or both; neurologic symptoms; psychiatric disorder; and hepatic events).

Literature Search Strategies

We conducted an electronic literature search of the following databases: Cochrane Central Register of Controlled Trials, PubMed, EMBASE, Chinese Biomedical Database, China National Knowledge Infrastructure, and Chinese Scientific Journals Database. The studies included were written in English or Chinese. The references for each study which met the inclusion criteria were also scanned to identify any studies that were not included in the initial search. The following search terms were used as

medical subject headings: *interferon-α, cytosine arabinoside, cytarabine, chronic myelogenous leukemia* AND (*chronic myelocytic leukemia* OR *chronic granulocytic leukemia* OR *CML*).

DATA EXTRACTION

The following data were extracted by one reviewer (B.M.) and checked independently by the second reviewer (J.H.T.). We used predesigned forms to collected information about the IFN-alfa and Ara-C tested, the population studied (age, sex, and underlying conditions), treatment dosages and dosing schedules, the treatment effect at 6 months and 1 year, the specific measurement of this intervention (5-year survival rate or CRs), and the incidence of adverse effects and mortality according to causes of death.

ASSESSMENT OF METHODOLOGIC QUALITY

Study quality was assessed independently by 2 reviewers (L.Y.L. and Y.K.H.) and discrepancies were resolved by consensus. RCTs were evaluated by randomization, double-blinding, and withdrawal/follow-up according to the criteria of the *Cochrane Handbook for Systematic Reviews of Interventions*.[14] Allocation concealment was assessed as adequate, inadequate, or unclear.[15]

STATISTICAL METHODS

We quantitatively pooled the results of individual trials when possible. For dichotomous data, relative risk (RR) was calculated and used in description of the results. For continuous outcomes, a weighted mean difference was calculated when outcome measurements in all trials were performed on the same scale. A standardized mean difference was used when the trials were all assessed using the same outcome, but the outcome was measured in a variety of ways. Effects were considered statistically significant if $P < 0.05$. A z-test was used as statistically significant to test the differences in treatment effect between groups.[16] For each study, the most adjusted P value or RRs, with their 95% CIs, were used.

Heterogeneity was assessed using the χ^2 test and I^2 test. We set the statistical level of heterogeneity (χ^2 P) at 0.05 and considered an I^2 value $>50\%$ to indicate substantial heterogeneity.[17] We assessed any identified heterogeneity in an effort to explain it. If we were unable to find an explanation, such a finding was stressed in the review and highlighted that caution in the interpretation of these data was appropriate. When we found that a cause for heterogeneity was apparent and justified a separate analysis of the studies with a particular characteristic, such analysis was undertaken and presented. When we found no heterogeneity, the studies were included in a meta-analysis for the outcomes selected here. A random effects model was preferred where there was marked heterogeneity ($I^2 > 50\%$), and a fixed effects model was preferred in other circumstances. Statistical pooling of results was performed using standard meta-analysis software (RevMan 5.0; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). We planned to assess the possibility of publication bias using the funnel plot method[18] for the primary end points.

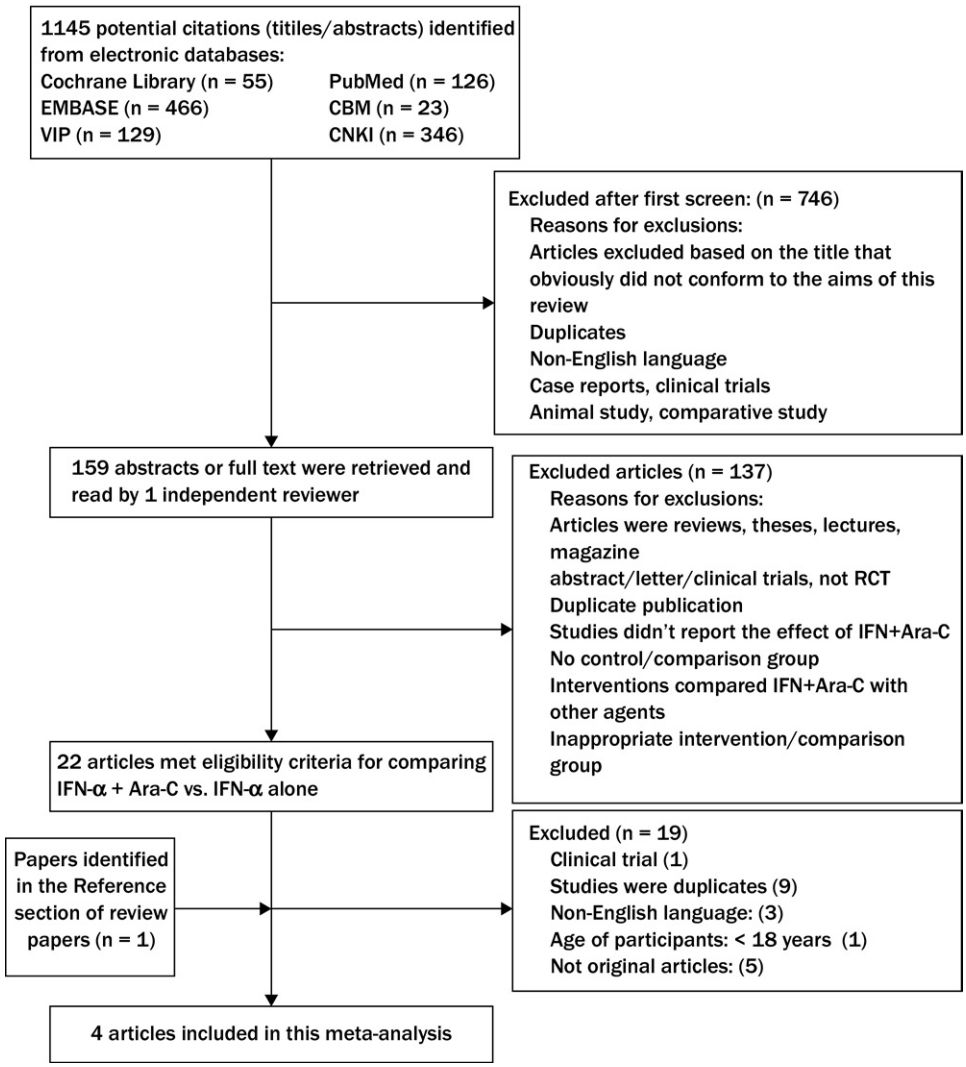

Figure 1. Study identification and selection process. Flow chart provides numbers of randomized controlled trials (RCTs) identified, excluded for various reasons, and included in the systematic review and meta-analysis. VIP = Chinese Scientific Journals Database; CBM = Chinese Biomedical Database; IFN-alfa + Ara-C = interferon alfa + cytarabine; CNKI = China National Knowledge Infrastructure.

RESULTS

Description of Studies

The literature searches yielded a total of 1145 potentially relevant citations. The selection process is illustrated in Figure 1. The 4 randomized controlled trials[19–22]

included involved 3139 patients, of whom 1583 were allocated to receive IFN-alfa + Ara-C therapy and 1556 were assigned to receive IFN-alfa alone.

Methodologic Quality of Included Studies

The characteristics of the 4 included studies are summarized in the **Table**. Only 1 study[19] explicitly described the randomization process and involved adequate allocation concealment with an intention-to-treat analysis. The population sizes in these 4 studies ranged from 538 to 1340, and the duration of follow-up ranged from 6 months to 5 years.

Publication Bias

Overall, there was no apparent asymmetry in the funnel plots (**Figure 2**) when evaluating our publication bias, and no significant publication bias was detected in our meta-analysis.

Assessment of Clinical Effectiveness

All 4 articles reported information on CHR compared between an intervention group and a control group. The CHR in the IFN-alfa + Ara-C arm was 68% (1082 of 1583 patients) compared with 60% (927 of 1556 patients) in the IFN-alfa arm. The summary RR was 1.15 (95% CI, 1.09–1.21). Heterogeneity was not detected among these studies ($P = 0.46$; $I^2 = 0\%$).

Figure 3 presents detailed data related to subgroup CR for all 3043 available participants in all 4 studies.[19–22] Tests of heterogeneity were not significant (CCR, $P = 0.69$, $I^2 = 0\%$; PCR, $P = 0.54$, $I^2 = 0\%$; MCR, $P = 0.93$, $I^2 = 0\%$). CCR RR (fixed-effect model) was 1.87 (95% CI, 1.47–2.38), PCR RR was 1.48 (fixed-effect model) (95% CI, 1.25–1.75), and MCR RR was 1.61 (fixed-effect model) (95% CI, 1.42–1.83); these findings showed statistically significant improvements in favor of the combination study regimen compared with treatment with IFN-alfa alone.

Figure 4 presents a trend in favor of combination treatment compared with treatment with IFN-alfa alone. By implementing subgroup analysis, 3-year overall survival was 86% (548 of 635 patients) compared with 79% (497 of 626 patients) in 2 studies,[20,21] with an RR (fixed-effect model) of 1.09 (95% CI, 1.03–1.14); 5-year overall survival was 69% (626 of 910 patients) compared with 63% (565 of 887 patients) in the other 2 studies,[19,22] with an RR (fixed-effect model) of 1.08 (95% CI, 1.01–1.15). No statistical heterogeneity existed in the 2 subgroups ($P = 0.38$, $I^2 = 0\%$; and 0.61, $I^2 = 0\%$ separately).

Secondary Outcome Measures

Three individual trials[19,20,22] reported different types and frequency of adverse events (represented in **Figure 5**). The combined therapy involved a higher incidence of hematologic toxicity, gastrointestinal adverse events such as nausea, vomiting, and diarrhea, and severe mucositis (RR [fixed-effect model] = 2.63 [95% CI, 1.94–3.56]); RR [fixed-effect model] = 3.38 [95% CI, 2.28–5.00]); and RR [fixed-effect model] = 8.84 [95% CI, 3.82–20.46], respectively). The occurrence of weight loss and skin rash was observed more frequently in the IFN-alfa + Ara-C group compared with the IFN-alfa

Table. Clinical characteristics and methodologic quality of the included studies.

Study/ Year	No. of Participants		Intervention (dose and schedule)		Outcome Measures	Randomization	Allocation Concealment	Blinding	Withdrawal/ Follow-up
	IFN-Alfa/ Ara-C	IFN-Alfa	IFN-Alfa/Ara-C	IFN-Alfa					
Guilhot et al,[20] 1997	360	361	IFN-alfa-2b: initial dose 5 MU/m^2 SC Ara-C: 20 mg/m^2 in a single daily dose for 10 d SC	IFN-alfa-2b: initial dose 5 MU/m^2 SC	CHR (6 mo) CR (12 mo), MCR, CCR, PCR SR (3 y) Adverse effects	Adequate	Adequate	Not reported	Yes, ITT analysis was performed
Kantarjian et al,[21] 2000	275	265	IFN monthly courses of cytarabine	IFN	CHR (6 mo) CR (12 mo), MCR, CCR, PCR SR (3 y)	Unclear	Unclear	Not reported	Yes
Baccarani et al,[19] 2002	275	263	hrIFN-alfa-2a: 3^6 IU/d, first 2 wk; 6^6 IU/d, the next 2 wks; 5^6 IU/m^2/d SC/IM LDAC: 40 mg/d the first 10 d of each mo	hrIFN-alfa-2a: 3^6 IU /d, first 2 wk; 6^6 IU/d, the next 2 wks;5^6 IU/m^2/d, thereafter, SC/IM	CHR (6 mo), the time to achieve CHR CR (12 mo /24 mo), MCR, CCR, PCR SR (5 y), its 95% CI Adverse effects	Unclear	Unclear	Not reported	Yes
Pingoy et al,[22] 2003	673	667	LDAC added to the standard IFN-alfa protocol	IFN-alfa	CHR (6 mo) CR (12 mo), MCR, CCR, PCR SR (5 y) Adverse effects	Unclear	Unclear	Reported	Yes

IFN-Alfa + Ara-C = interferon alfa + cytarabine; CHR = complete hematologic response; CR = cytogenetic response; MCR = major cytogenetic response; CCR = complete cytogenetic response; PCR = partial cytogenetic response; SC = subcutaneously; SR = survival rate; hr = human recombinant; IM = intramuscularly; ITT = intention-to-treat analysis; LDAC = low-dose cytarabine.

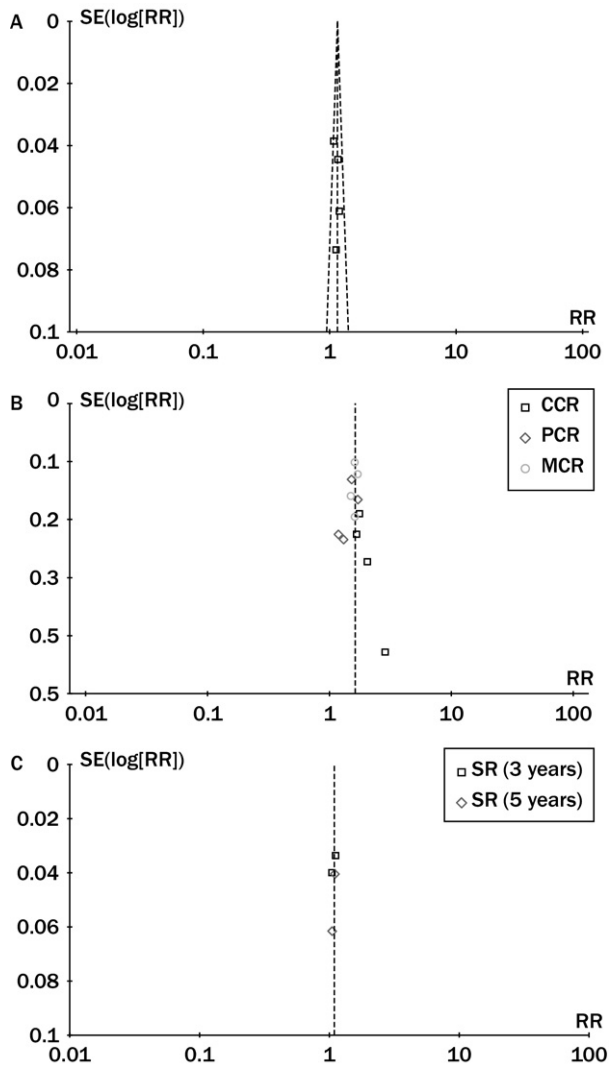

Figure 2. Funnel plots of (A) complete hematologic response (CHR); (B) cytogenetic response (CCR = complete cytogenetic response; PCR = partial cytogenetic response; MCR = major cytogenetic response); and (C) survival rate (SR). RR = relative risk.

alone group (RR [fixed-effect model] = 2.00 [95% CI, 1.47–2.73] and RR [fixed-effect model] = 3.75 [95% CI, 2.13–6.59], respectively). However, other adverse effects—such as fever, flu-like syndrome or both, neurologic symptoms, psychiatric disorder, and hepatic events—manifested no statistical differences. Heterogeneity was not detected among subgroups except with respect to weight loss ($P = 0.11$; $I^2 = 55\%$).

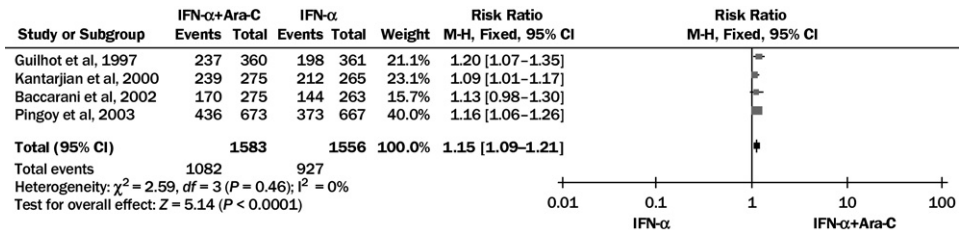

Figure 3. Randomized controlled trials of complete hematologic response (CHR). IFN-alfa + Ara-C = interferon alfa + cytarabine; M-H = Mantel-Haenszel method; RR = relative risk. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance.

DISCUSSION

Adult patients with chronic-phase CML were investigated in this meta-analysis, which found that use of the IFN-alfa + Ara-C regimen resulted in a statistically significant advantage in CHR rate.

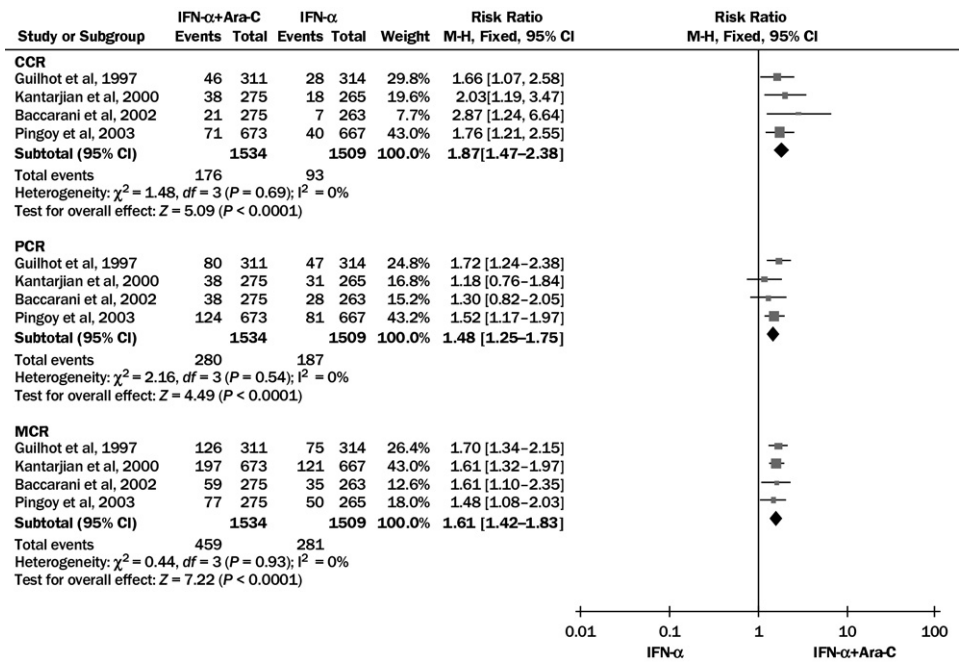

Figure 4. Randomized controlled trials of cytogenetic response. IFN-alfa + Ara-C = interferon alfa + cytarabine; CCR = complete cytogenetic response; PCR = partial cytogenetic response; MCR = major cytogenetic response; RR = relative risk. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance.

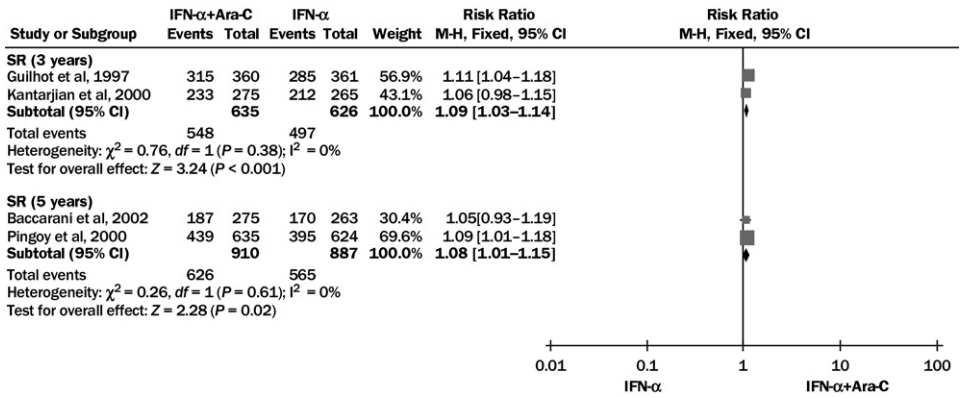

Figure 5. Randomized controlled trials of overall survival rate (SR). IFN-alfa + Ara-C = interferon alfa + cytarabine; RR = relative risk. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity rather than chance.

In a subgroup analysis of CR rates at 12 months, a statistically significant improvement was found in MCR, CCR and PCR values. This finding appears to be in accordance with controlled clinical clamp studies,[23,24] which demonstrated in a multivariate analysis that a CR achieved with IFN-alfa + Ara-C was independently associated with improved survival. In terms of overall survival rate, the results obtained from this meta-analysis were comparable in both the IFN-alfa + Ara-C arm and IFN-alfa monotherapy arm. However, although the results discussed here came from only 4 RCTs, we reported a statistically significant benefit in CHRs, CRs, and 3- or 5-year survival rates, which could be used to determine clinical significance for the chronic phase of CML.

Throughout our extensive literature search, we did not identify any trials involved in the treatment of accelerated phase or blast crisis patients for comparison of the combination therapy versus single IFN-alfa only. Ferrajoli et al[25] reported that patients with late chronic and accelerated phase CML benefit from combined IFN-alfa + ARA-C treatment and achieve hematologic and cytogenetic responses not obtained during previous treatment without being exposed to undue toxicity. Therefore, it is unknown whether the use of IFN-alfa + Ara-C will attain the same or higher cytogenetic remission results in the accelerated phase or blast crisis.

The frequency of adverse events of the 2 drugs differed significantly between the combination arm and the IFN-alfa arm, which suggests that combination treatment can cause more adverse effects for patients with CML. A total of 80% of the studies provided at least some information on adverse events. Overall, the reported frequency and type of adverse events (local site reactions and hematologic toxicity) and discontinuation rate were comparable between the combination arm and the IFN-alfa alone arm. Data on the incidence of serious adverse events episodes are limited. In terms of hematologic toxicity, adequate measurements indicators include leukopenia, neutropenia, and thrombocytopenia. There was only 1 original RCT[20] that specified the

absolute level of thrombocytopenia, which in the IFN + Ara-C arm was >2 times that observed after treatment with IFN alone (20 vs 8). Patients who received combination treatments exhibited a higher occurrence of nonhematologic toxicity, including nausea, vomiting, diarrhea, mucositis, weight loss, and discomfort with an additional subcutaneous injection. We were not able to identify increased severity or frequency of adverse effects caused by IFN-alfa or Ara-C because patients were administered different dosages of 1 or 2 drugs and subjected to varying medication regimens. IFN-alfa was administered in all study protocols with a wide dose range between 5 MU/m^2 and 5 ^{6}IU/m^2. Daily doses of Ara-C in the studies discussed here range from an absolute dose of 20 mg to 40 mg/m^2.

LIMITATIONS AND IMPLICATIONS OF RESEARCH

This review summarizes the large body of literature comparing the effects of IFN-alfa + Ara-C versus IFN-alfa alone for patients with CML in the chronic phase. However, there are several limitations that must be addressed. First, this effort included studies written only in English or Chinese, which may not be representative of the entire literature available. We should be particularly concerned about publication bias in settings that do not foster English or Chinese language use. The risk of having missed or overlooked trials in this setting was substantial, as assessed by tests for publication bias and funnel plot. The analysis revealed no obvious publication bias in our study, which suggests that publication bias was unlikely to be an important factor. However, the limited number of trials in each of the comparisons makes assessment of publication bias difficult. The results may be affected due to the limited number of studies included. Second, a common shortcoming of the quality in the trials was the inadequate description of the randomization and blinding procedures, as well as the absence of intention-to-treat analyses. Third, other important weaknesses were the very poor description of dropouts and of harm-related issues (eg, only 1 trial[20] reported all of the causes of death for each study arm). Finally, outcome data from the original publication could not be included in the analysis for methodologic reasons (eg, no separate analysis for 3- and 5-year survival rates provided). Unfortunately, communications with the authors did not substantially improve the data quality. Few authors submitted the original data that we requested. Additionally, another concern was that patients enrolled in this study admitted to receiving allogeneic bone marrow transplantation or autologous stem cell transplantation at any time that they had appropriate donors, so loss to follow up was inevitable during the entire course of treatment.

Based on the limits of this meta-analysis, future research efforts should focus on large, well-designed studies. Long-term follow-up data from the first- and second-line IFN- or Ara-C–based trials are critical to determine the effect on survival, duration of response, and development of resistance. Research is also needed into specific subgroups, such as accelerated or blast phase of CML patients, the elderly, children, or those eligible for bone marrow transplantation. Further investigation of IFN-alfa + Ara-C on quality of life is important, especially in terms of evaluating societal values. More detailed economic studies are also required to aid appraisal of the

2 drugs used in single-agent treatment or in combination with other therapies to help provide cost-effective guidelines.

CONCLUSIONS

In patients with the chronic phase of CML, the available evidence from the literature was sufficient to make several conclusions. Ara-C combined with IFN-alfa significantly improved CHR and CR rates as well as prolonged 3- and 5-year survival compared with IFN-alfa alone. Combination therapy was more likely to cause serious adverse effects, and the reported methodologic quality of included studies was generally poor to intermediate. Therefore, from this meta-analysis, the regimen of IFN-alfa + Ara-C may be the first choice for CML patients who live in developing countries, given the superiority of imatinib. Given further safety concerns, we need a long-term follow-up study enrolling large numbers of patients who use combination treatment. Also needed are well-designed studies of accelerated or blast phase diseases to determine the safety profile for both these drugs.

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